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TITLE: Acustimulation for the Control of Chemotherapy-Induced
Nausea in Breast Cancer Patients

PRINCIPAL INVESTIGATOR: Joseph A. Roscoe
Gary R. Morrow, Ph.D.
Peter Bushunow

CONTRACTING ORGANIZATION: University of Rochester
Rochester, New York 14627

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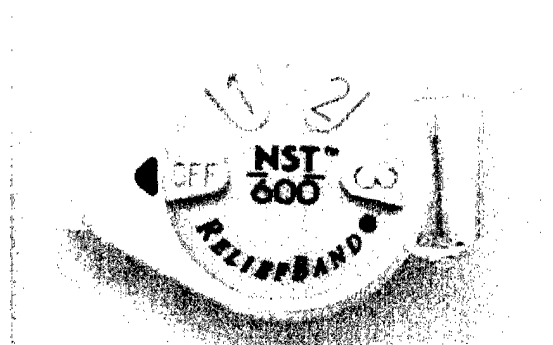
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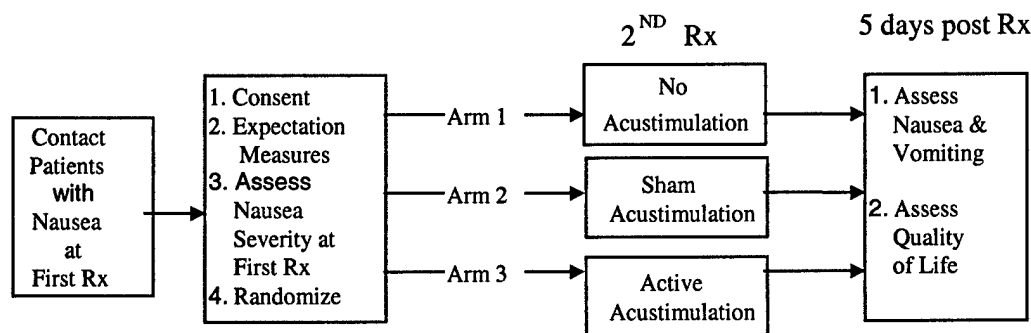
Introduction

The current experiment examined the efficacy of acustimulation (mild electrical stimulation to an acupuncture point) to the Neiguan (P6) acupuncture point (located on the ventral surface of the wrist) in controlling chemotherapy-induced nausea and vomiting (NV). In traditional Chinese medicine, this acupuncture point is associated with NV relief. It was a randomized three-arm clinical trial testing the usefulness of an acustimulation wrist band for the relief of chemotherapy-induced nausea and vomiting as an adjunct to standard 5-HT₃ antiemetics. Patients who experienced nausea at their first treatment were eligible to participate. Patients in the two treatment groups (i.e., correct location: band worn on the inside of the wrist and sham location: band worn on the outside of the wrist) put on the acustimulation wrist band prior to the administration of chemotherapy and wore it for up to five days. The use of an active acustimulation band in the sham condition was intended to control for both the placebo effect and for any effect due to the release of endorphins, thereby allowing for a direct examination of the efficacy of stimulation to the (P6) acupuncture point. In addition, the experiment had a "no band" condition for additional comparisons.



ReliefBand®, Woodside Biomedical, Carlsbad, CA

STUDY SCHEMA



Hypothesis: Acustimulation to the Neiguan (P6) acupuncture point will be efficacious in controlling both delayed and acute chemotherapy-induced NV.

Primary Question: Can an acustimulation wrist band reduce the nausea and emesis that occurs on the day of chemotherapy treatment (acute) and that occurring on days 2 - 5 following treatment (delayed)?

Secondary Question: Is any effectiveness found for acustimulation related to patient expectancies of the effectiveness of the wrist band?

Body

Status of tasks listed in the Statement of Work:

Task 1: Month 1: Prepare treatment protocols and obtain IRB approval

Status: Completed, the study was approved and open to accrual at four locations. Two of the sites, Highland Hospital Cancer Center and Strong Memorial Hospital Cancer Center, are under the governing IRB at Strong Memorial Hospital. The remaining two, Rochester General Hospital Cancer Center and the Genesee Hospital Cancer Center, are under the governing IRB of VIA Health.

Task 2: Month 1: Present study protocol to clinic staffs at all study sites.

Status: Completed, the study was presented to the clinic staff at four locations.

Task 3: Month 1: Prepare intervention materials and questionnaires.

Status: Completed. A copy of the one-page instruction sheet that we gave patients and the study measures were attached in a previous report.

Task 4: Months 1-34: Collect preliminary data on subjects screened for entry into the randomized study

Status: Completed. As part of our accrual process, we examined clinic schedules at the Highland Hospital Cancer Center, the Strong Memorial Hospital Cancer Center and the Rochester General Hospital Cancer Center in order to identify patients who had one cycle of chemotherapy and who were eligible for our study. We then contacted the patient's oncologist for permission to talk to the patient about the study.

Task 5: Months 1-34: Randomize eligible patients who have signed a consent form to group assignment (target accrual = 107 patients).

Status: Completed, 107 patients were accrued and randomized to the protocol. Of the 107 patients, 96 completed the study and provided evaluable data, 10 patients did not return any data and the data from one patient was incomplete. Accrual and evaluable patients per treatment arm are as follows:

Arm 1 - Accrual = 36 - Evaluable = 33

Arm 2 - Accrual = 37 - Evaluable = 31

Arm 3 - Accrual = 34 - Evaluable = 32

We anticipated that that 5% or 5 of the targeted 107 patients would not provide evaluable data. With our accrual complete we had a total of 11 unevaluable patients (10% of those accrued). We consider this within the acceptable range.

Task 6: Months 1-34: Carry out the study.

Status: Completed

Task 7: Months 1-34: Monitor daily clinic schedules at all study sites (oncology departments in three Rochester hospitals) to insure timely accrual of subjects for the study.

Status: Completed

- Task 8: Months 1-34: Review progress of study and address any problems as they arise.
Status: Completed, no problems arose.
- Task 9: Months 1-34: Complete required annual reports.
Status: Completed
- Task 10: Months 1-34: Edit, verify and input data as they are collected.
Status: Completed, the data from 107 patients has been entered into an Access data base.
- Task 11: Months 35-36: Analyze results according to data analysis plan.
Status: Completed, see the Results Section in the final report below.
- Task 12: Months 35-36: Write final report and complete fiscal accounting.
Status: Completed

Introduction

The 5-HT₃ antagonists (Zofran®, GlaxoSmithKline, Research Triangle Park, NC) and granisetron (Kytril®, Roche Laboratories, Inc., Nutley, NJ), in widespread use since the early 90's, are more effective than prior medications in preventing chemotherapy-induced vomiting.¹⁻³ However, chemotherapy-related nausea is not as well controlled by these drugs and remains a significant problem.³ As many as 80% of patients who received chemotherapy experience nausea to some degree, with up to 40% having at least one episode of vomiting.³ In a recent study published by our group, 76% of 322 patients who received chemotherapy regimens containing cisplatin, carboplatin or doxorubicin experienced nausea following their first treatment. Of these 322 patients, 147 (46%) had nausea of moderate severity or greater.⁴ Nausea and vomiting (NV) not only seriously detract from quality of life (QOL),⁵⁻⁷ but also can interfere with adherence to treatment regimens or cause oncologists to reduce chemotherapy doses.⁸⁻¹⁰ In addition, there is no known pharmacological agent that effectively treats the delayed nausea that occurs/develops 2-5 days post chemotherapy.^{9,11} Hence, identifying methods to successfully prevent and alleviate treatment-related nausea is of critical importance.

The complementary and alternative medicine treatment of acupuncture point stimulation may help in alleviating this persistent and troublesome problem. Stimulation of the P6 acupuncture point that is located on the inside of the wrist with needles (acupuncture) or pressure (acupressure) has been used to relieve NV in traditional Chinese medicine for over 23 centuries.¹² Recent literature reviews indicate that acupuncture and acupressure may provide relief from these symptoms.¹³⁻¹⁵ Specifically, needling or applying pressure (generally with an acupressure band such as the SeaBand, Sea Band UK Ltd., Leisestershire, England) to an acupoint have shown efficacy in alleviating morning sickness,¹⁶⁻¹⁹ motion sickness,^{20,21} post-surgical nausea,²²⁻²⁸ and NV associated with chemotherapy.^{29,30}

Beginning in the early 90's, studies assessing the efficacy of mild electrical stimulation (acustimulation) using portable TENS wrist bands to the P6 acupuncture point for control of nausea have also been conducted. All of these studies used the ReliefBand® (Figure 1; Woodside Biomedical, Carlsbad, CA) which is marketed for this purpose and has FDA clearance for treatment of nausea and vomiting due to pregnancy, motion sickness, chemotherapy, and as an adjunct to antiemetics for post-operative nausea. Positive findings have been found for the

efficacy of acustimulation bands in controlling motion sickness,³¹ morning sickness,³²⁻³⁵ and postoperative nausea.³⁶⁻³⁸

A literature review revealed five publications on the efficacy of acustimulation bands for the treatment of chemotherapy-induced nausea. Treish and colleagues³⁹ conducted a randomized study in which 50 patients wore either active or placebo acustimulation bands for five days after chemotherapy as an adjunct to standard antiemetic medications. Those wearing the active band reported significantly less nausea and significantly fewer episodes of vomiting compared to patients wearing the placebo bands. Pearl and colleagues⁴⁰ conducted a randomized, double blind, placebo-controlled experiment with a follow-up crossover trial. Of the 18 patients completing the crossover portion of the study, those who wore the active band, as compared to the placebo band, reported significantly less severe nausea on the second through fourth post-treatment days.

The three other studies examining the efficacy of acustimulation bands for control of chemotherapy-induced nausea were conducted by our own research group. In the first of these studies, we found results that closely approached conventional levels of statistical significance ($P < .06$) when the efficacy of the bands in reducing the severity of delayed nausea were compared to no bands in 27 chemotherapy recipients who had experienced nausea after their first treatment.⁴¹ This finding must be interpreted with particular caution, however, because of weaknesses associated with the 3-level crossover design used in the study. Our second study was a non-controlled, open-label, trial in which we gave Reliefbands® to 42 patients who had nausea at their previous two chemotherapy treatments.⁴² Of the 29 patients who completed the optional feedback questionnaire following treatment, 16 patients said the band was somewhat or very helpful in reducing nausea.

Finally, our group also directly compared the effectiveness of acustimulation bands with acupressure bands as an adjunct to 5-HT₃ receptor antagonist antiemetics given as part of routine care.³⁰ A total of 739 (male = 57) chemotherapy naïve patients scheduled to begin either cisplatin or doxorubicin-based treatment were randomly assigned to wear bilateral Sea-bands®, one Reliefband®, or no band. Analyses were conducted separately for males and females because of pronounced gender differences. Fewer men vomited in the Reliefband® (16%) compared to the no band (50%) conditions, $P = .03$. They also experienced less nausea on the day of treatment and less nausea overall, $P_s < .05$. There were no significant differences on any measures between the acustimulation and the acupressure treatment conditions. By contrast, the acustimulation band was not helpful for women. The reduction in nausea on the day of treatment in the acupressure band compared to the no band condition, however, closely approached statistical significance, $P = .052$. Interestingly, when expected efficacy of the wrist bands was considered, differences in nausea development were observed in women assigned to the acupressure condition, but not for those in the acustimulation condition and not in men. Women who received the acupressure bands and expected them to be effective ($N = 99$) experienced less nausea on the day of treatment and also less overall nausea compared those who did not expect them to be effective ($N = 113$) and to the no band control group ($N = 214$), $P_s < .05$.

We add to this somewhat mixed literature on the effectiveness of acustimulation bands with a randomized three-arm clinical trial examining the efficacy of the Reliefband® for the control of chemotherapy-induced nausea as an adjunct to standard 5-HT₃ antiemetics. The use of an active acustimulation band in the sham location condition was intended to control for both the placebo effect and for any effect due to the release of endorphins, thereby allowing us to directly examine

the efficacy of acupuncture point stimulation. In addition, the experiment had a "no band" condition for additional comparisons.

Methods

Patients

Women 18 years of age or older who were treated at one of four Rochester area cancer centers with doxorubicin-based chemotherapy for breast cancer and experienced nausea and/or vomiting after their first chemotherapy cycle were eligible to participate in the study. Patients with clinical evidence of bowel obstruction, symptomatic brain metastases or who were using a cardiac pacemaker or undergoing concurrent radiotherapy or interferon treatment were excluded. Written informed consent was obtained from each subject and the Institutional Review Board of each participating site approved the protocol.

Procedures

To encourage patient participation and promote patient confidence in the project, the medical oncologist of each potential participant assessed the patient's level of nausea after the first chemotherapy cycle and briefly explained the study to eligible patients. She/he then introduced the patient to the study personnel, all of whom had been trained in the proper use of the Reliefband®. The study was discussed with patients at a physician visit prior to their second chemotherapy cycle. Participants who signed the consent form were immediately randomized to one of three treatment arms. Patients assigned to wear the band in the sham location placed it on the outside of the wrist approximately 2 inches from the crease of the wrist. Those assigned to wear it in the correct location placed it on the inside of the wrist, approximately 2 inches from the crease of the wrist joint between the tendons of the palmaris longus and flexor carpi radialis muscles.

All patients assigned to wear an acustimulation band were told they could adjust the intensity of the stimulation by turning the dial to whatever one of 5 intensity settings, ranging from 10mA to 35mA, they felt was the most comfortable and/or effective. They were also told to avoid letting the band come into contact with water, and they could wear the band on either wrist, provided the arm was not affected by lymphedema. Patients were instructed to wear the band as much or as little as they wanted or needed to over the five days of the study, and to record the approximate number of hours they wore the band.

All patients received a standard antiemetic prophylaxis, which included a 5-HT₃ receptor antagonist antiemetic on the day of treatment. Dexamethasone or other cortical steroids were allowed, as were all ancillary treatments as appropriate for control of symptoms of the cancer or the side effects of its treatment. All antiemetic medications taken following treatment were recorded in a medication log maintained by the patient.

Measures

At the time of consent, patients provided demographic information and details concerning prior experience with NV, e.g., nausea during pregnancy, susceptibility to motion sickness, etc. Patients were also asked to describe their nausea at its worst following their last treatment, as well as what they thought their level of nausea at its worst would be following the current treatment. The possible responses for each of these two questions were "very mild or none at all," "mild," "moderate," "severe," "very severe," and "intolerable" and were coded 1 - 6, respectively. A question, used previously by our group,^{1,2} as well as by others,³ directly assessed

patients' expectations of developing nausea on a 5-point Likert scale, anchored at one end by 1 = "I am certain I will not have this," and at the other end by 5 = "I am certain I will have this."

Expected efficacy of the Reliefband® was assessed, following a one-minute trial application of the band turned on and placed in the randomized position, using a 5-point scale anchored at one end by 1 = "Not at all effective" and at the other end by 5 = "Very effective."

Nausea and emesis were measured by a patient report diary developed by Burish⁴ and Carey⁵ and completed by patients over a five-day period. Each day was divided into four segments (morning, afternoon, evening, night) in which patients report the severity of nausea and number of vomiting episodes for each period on the day of treatment and on the four following days (20 total reporting times). Severity of nausea was assessed on a 7-point rating scale, anchored at one end by 1 = "Not at all nauseated" and at the other end by 7 = "Extremely nauseated." Anti-nausea medication use and number of vomiting episodes were recorded for the same time intervals as part of the diary. Additional questions concerning use of and recommendations for the acustimulation band were added to the measure.

Quality of life (QOL) was assessed using the Functional Assessment of Cancer Therapy Scale-General (FACT-G). The FACT-G is a 28-item scale (higher scores = better QOL) developed specifically for use in cancer clinical trials.⁶ It was developed by Cella and his group through extensive interviews with patients experiencing symptoms of cancer and with oncology professionals. It has shown very good test-retest reliability as well as validity.⁷ Patients completed the measure four days after the day of chemotherapy and assessed QOL retrospectively since the treatment.⁸

Participants were given the latter two questionnaires to complete at home and with instructions to mail them back in the stamped, pre-addressed envelopes that were provided. Reminder phone calls were made to patients, if necessary.

Planned Analyses

The primary outcome variable for this study was the severity of nausea averaged across days 2 - 5 of treatment, i.e., delayed nausea. Analysis of variance (ANOVA), with a significance level of 0.05, was used to compare the average nausea severity in the three treatment arms. We intended to compare the sham location group to the correct location group if the analysis was significant. Secondary study outcomes were the severity of nausea during the first 24 hours following chemotherapy (acute nausea) and the occurrence of vomiting during the same 24-hour period. Data for acute nausea will be analyzed in the same way as delayed nausea. Occurrence of vomiting was analyzed using a logistic regression model parallel to the ANOVA model used to analyze severity of nausea. All analyses were done on an intent-to-treat basis.

A further objective of this study was to investigate the relationship between expectations about the development of chemotherapy-related nausea and vomiting and its later occurrence and severity, as well as to determine if expected efficacy of the acustimulation band was related to actual band efficacy. In addition to the above, exploratory analyses were planned with QOL as the outcome variable.

Results

Patient Sample

Ninety-six (90%) of the 107 patients randomized to the study provided evaluable data. Of these 96 patients, 87 were Caucasian, 8 were African-American, and one participant self identified as "other". Age ranged from 28-72, with a mean of 49.5 and most (72%) were married. Thirty-three patients were randomized to the control condition (no band); 31 were assigned to the incorrect location condition (outside of wrist); and 32 were randomized to wear the band in the correct location (inside of wrist). All study subjects received their treatments as outpatients. Eighty-nine of the 96 patients took some type of antiemetic following treatment; 6 took none, and the data from one patient regarding antiemetics is missing.

Analysis of variance showed that the three study arms did not differ significantly on susceptibility to motion sickness, nausea during pregnancy (1 = yes, 0 = no or not applicable), optimism, or on any of our other questions relating to susceptibility to NV, all P s > 0.1.

Despite randomization, the groups did, however, differ on age

(mean_{no band} = 50.6, mean_{sham} = 45.4, mean_{correct} = 52.4, P = .008) and on the degree of nausea experienced following the prior treatment (mean_{no band} = 4.0, mean_{sham} = 3.2, mean_{correct} = 3.0, P < .001). These two variables were, therefore, used as covariates in all analyses examining outcome difference between treatment arms.

Treatment Effects

Four outcomes related to wrist band efficacy (acute nausea, delayed nausea, any vomiting, and QOL) were examined using analysis of covariance (ANCOVA) controlling for age and past nausea severity. There were no significant differences on any of these study measures among the three treatment conditions, all P s > 0.1. (Table 1)

Table 1. Comparison of Study Outcomes by Randomization Condition

	<u>No Band</u> (N = 33) Mean (SE)	<u>Sham Location</u> (N = 31) Mean (SE)	<u>Correct Location</u> (N = 32) Mean (SE)
Delayed nausea ¹	2.8 (.23)	2.4 (.23)	2.6 (.23)
Acute nausea ²	2.4 (.28)	2.2 (.28)	2.2 (.28)
QOL	71.1 (2.4)	77.6 (2.4)	75.4 (2.4)
Vomiting ³	39%	26%	44%

Notes: Differences between groups are not statistically significant, all P s > 0.1; values reported for nausea and QOL are estimated marginal means (controlling for age and nausea severity from the prior treatment); ¹ average for treatment days 2-5; ² average for Day 1 of treatment; ³ proportion of patients who vomited.

Treatment Effects by Expected Band Efficacy

A t-test for independent samples showed that mean expected efficacy for the acustimulation bands using the full 5-point scale did not differ by randomization location ($\text{mean}_{\text{sham}} = 3.45$, $\text{mean}_{\text{correct}} = 3.47$, $P = 0.9$). Similarly, expected efficacy for the device was not significantly correlated with age, $r = .02$, nor with "Past N Worst", $r = -.09$, both P s > 0.3 . Because no differences were observed in actual or expected band efficacy related to band placement location, the two trial arms receiving the bands were combined and a new grouping for these patients, based upon expected band efficacy, was made. The 26 patients who indicated a response of either "4" or "5" on the expected efficacy question were coded as "high expected efficacy" and the remaining 37 patients receiving the acustimulation bands were coded "low expected efficacy." Differences in the study outcome variables (acute nausea, delayed nausea, any vomiting, and QOL) between these two groups were then examined using t-tests for independent samples. No statistically significant differences between groups were observed, all P s > 0.5 .

Satisfaction with Band and Duration of Use

Overall satisfaction with the acustimulation bands appeared to be high with over a third of the patients wearing the band for over 48 hours (the longest of the five "duration of time worn" categories on the feedback questionnaire) and over 60% wearing the band at least 24 hours. The proportion of patients wearing the bands at least 24 hours was somewhat higher in the correct location compared to the sham location group (72% vs 53%). Overall patient satisfaction with the band was moderate as assessed by the feedback question asking whether they would recommend it to other patients. The mean response on this 5-point scale (anchored at one end by 1 = "Strongly do not recommend" and at the other end by 5 = "Highly recommend") was 3.3. The slight difference in strength of recommendation by location (means: sham = 3.2, correct = 3.4, was not statistically significant, $P = .34$).

Discussion

Our study results do not support our hypothesis that acustimulation bands are efficacious as an adjunct to pharmacological antiemetics for control of chemotherapy-related nausea in female breast cancer patients. No statistically significant differences between groups related to acustimulation band use were observed in any of our four outcome measures (i.e., delayed nausea, acute nausea, vomiting, and QOL). This finding is in keeping with the results of our multi-center study, which ran concurrently with this one, comparing the efficacy of acupressure bands with acustimulation bands for control of chemotherapy-induced nausea. This study, as discussed previously, also found no evidence that the acustimulation bands were beneficial to women. Interestingly, while not helpful for women, the device was found helpful to men. Please refer to our article on that study for a discussion of this point.⁹

Our findings that the acustimulation bands were not helpful in the current study held true even for the women who thought the bands would be efficacious. The 26 women who received an acustimulation band and expected the device to be helpful fared no better than the 37 women who received a band and held neutral or negative expectancies. Expectation of efficacy for a treatment, thought to be a primary component of the placebo effect,^{10,11} has been related to the efficacy of acupressure bands^{9,12,13} and could reasonably be expected to be related to acustimulation band efficacy. The finding that control of NV did not improve even for the subgroup of women who expected the acustimulation bands to be effective is in keeping with the results of the above mentioned multi-center study. The apparent placebo effect associated with

use of the acupressure bands found in that study was not present for women receiving the acustimulation bands.⁹

While the negative results from the current study concerning acustimulation band efficacy are in complete agreement with the findings from the sub-group of women in the multi-center study who received the device, they are difficult to reconcile with other published research. All of the other published research reported efficacy for the device in controlling at least some aspect of nausea or vomiting. Adding to this perplexity is the fact that the acustimulation band, while not efficacious for women in the multi-center study, was very helpful for men. While evidence from the multi-center study suggests the existence of a gender difference, this is certainly not the only factor involved as no other investigation examining acustimulation bands reported a gender effect and several of the prior positive studies had only females as participants.¹⁴⁻¹⁸

The etiology of the nausea of study participants is a possible factor that may account for some of the discrepancy in acustimulation band effectiveness. Chemotherapy-induced nausea may simply be more difficult to control than nausea following surgery, from motion, or during pregnancy. This explanation fits with most of the published data as it is only in studies involving chemotherapy that the bands were found to be ineffective. Taking this line of reasoning one step further, is also possible that nausea from a given chemotherapy agent, i.e., doxorubicin, may not be amenable to control through acustimulation. Doxorubicin, a drug commonly given to breast cancer patients, is known to be a highly emetogenic drug,¹⁹ and all of the women in the current study and most of the women in the multi-center study received a relatively high dose of this agent. Few of the men in the multi-center study, even if they received doxorubicin, would have received as high a dose as the women received, because, typically, this drug is given in lower doses when used to treat other cancers. Unfortunately, the two other investigators examining acustimulation band efficacy in chemotherapy patients did not provide enough information in their reports to determine if the type of chemotherapy agent played a role in the efficacy of the device.^{17,20}

A seeming anomaly found in our results is the finding of no statistical benefit on our outcome measures even though patient acceptance of the acustimulation bands was generally high, as evidenced by the fact that more than 60% of the patients voluntarily wore the device for at least 24 hours. We speculate that this incongruity may in part be due to a potential quandary that can, in some circumstances, cause patients using the acustimulation bands to feel worse. The problem is that for patients who develop nausea despite the use of the acustimulation band, a negative conditioning effect can occur with the band becoming a reminder and reinforcer of their unpleasant state. This view is supported by our data from the multi-center showing that women randomized to wear the acustimulation band not only reported no benefit but actually reported significantly more nausea on Day 3 than patients in the control group.⁹ A simple way to avoid this potential conditioning problem, that we unfortunately did not do in either study, but would recommend for all patients receiving an acustimulation band, is to instruct them to take it off if nausea develops. They should then experimentally determine if the band is helpful by putting it back on after a short period of time and leaving it on only if they felt better with it on. Any conditioning effect present would then be positive in nature because wearing the band would then be associated with feeling better.

Key Research Accomplishments

All 12 research tasks have been successfully completed.

Reportable Outcomes

There have been no publications to date on these study findings. A manuscript, that is essentially the same as the above final report, is in the final stages of preparation and will be submitted to the *Journal of Alternative Therapies in Health and Medicine* before the end of September, 2003.

Conclusions

Study results did not support our hypothesis that acustimulation bands are efficacious as an adjunct to pharmacological antiemetics for control of chemotherapy-related nausea in female breast cancer patients. No statistically significant differences between groups related to acustimulation band use were observed in any of our four outcome measures (i.e., delayed nausea, acute nausea, vomiting, and QOL). No placebo/expectancy effect was observed as the acustimulation bands were not helpful in the current study even for the women who thought the bands would be efficacious.

Further research will be needed to determine if the effectiveness of the acustimulation band is dependant upon the specific cause of the nausea being treated and if there are specific chemotherapy agents or categories of patients, e.g., males, for whom the device is most effective.

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